Research on Environmental Health Interventions: Ethical Problems and Solutions

Accountability in Research 2005; 12: 69-101

David B. Resnik, J.D., Ph.D.*

Richard R. Sharp, Ph.D.**

Darryl C. Zeldin, M.D.*

*National Institute of Environmental Health Sciences, National Institutes of Health

**Center for Medical Ethics and Health Policy, Baylor College of Medicine

Address for correspondence: David B. Resnik, JD, PhD, Bioethicist, NIEHS, NIH, PO Box 12233, Mail Drop NH 06, Research Triangle Park, NC, 27709, U.S.A. Email: resnikd@niehs.nih.gov.

Phone: (919) 541 5658. Fax: (919) 541 3845.

Research on Environmental Health Interventions: Ethical Problems and Solutions

Word count: 12,089

David B. Resnik, J.D., Ph.D.*
Richard R. Sharp, Ph.D.**
Darryl C. Zeldin, M.D.*
*National Institute of Environmental Health Sciences, National Institutes of Health
**Center for Medical Ethics and Health Policy, Baylor College of Medicine

The ideas and opinions expressed in this article are the authors' personal opinions and do not represent the views of the National Institute of Environmental Health Sciences, the National Institutes of Health, or the U.S. government.

Abstract

This article reviews a variety of ethical issues that one must consider when conducting research on environmental health interventions on human subjects. The paper uses the Kennedy Krieger Institute lead abatement study as well as a hypothetical asthma study, to discuss questions concerning benefits and risks, risk minimization, safety monitoring, the duty to warn, the duty to report, the use of control groups, informed consent, equitable subject selection, privacy, conflicts of interest, and community consultation. Research on environmental health interventions can make an important contribution to our understanding of human health and disease prevention, provided that it is conducted in a manner that meets prevailing scientific, ethical, and legal standards for conducting research on human subjects.

Key words: environmental health research, Kennedy Krieger Institute, ethics, research methods

Introduction

Bioethicists, health policy analysts, and health care attorneys paid very little attention to ethical issues in research on environmental health interventions prior to the high-profile lawsuit, *Grimes vs. Kennedy Krieger Institute, Inc*. (*KKI*) (2001).[1] Before *Grimes*, most of the discussion of ethical issues in human subjects research focused on research involving medical interventions, such as clinical trials on new drugs, biologics, or medical devices. In *Grimes*, the goal was not to assess the safety and efficacy of a medical intervention but to assess an environmental intervention, lead abatement.[1] Most of the commentary on *Grimes* has focused on ethical issues related to exposing children to research risks and the interpretation of the federal regulations on pediatric research (see, for example, Kopelman 2002, Nelson 2002, Ross 2002; Hoffman and Rothenberg 2002). Although these are important questions to address, many other ethical issues arise in research on environmental interventions, such as balancing benefits and risks, risk minimization, safety monitoring, the duty to warn, the duty to report, the use of control groups, informed consent, equitable subject selection, privacy, and community consultation. All of these issues also occur in other research contexts, but environmental health research frames them in a different light and poses unique challenges. In this article, we will review, explore and discuss a variety of these issues and offer some guidance for researchers.

What is an environmental intervention?

In the last thirty years, biomedical researchers have focused on the biochemical, molecular, and genetic underpinnings of health and disease (Collins and McKusick 2001). Despite biomedicine's impressive gains in these areas, it remains important to pay close attention to role of environment in health and disease. Indeed, Francis Collins, Director of the National Human Genome Research Institute, which oversees the Human Genome Project, has recently called for a large study on the relationship between genes, health, and the environment, because the environment plays a key role in the development of most common diseases (Collins 2004). Changes in the environment can have dramatic effects on the health of entire populations. For example, access to clean water, sanitation, education, and food regulation are the most important factors in explaining the increases in longevity and decreases in infant mortality that took place in the world during the 20th century (Porter 1999). Also, it is often easier to impact human health through environmental changes than it is to affect health through other types of interventions, such as changes in lifestyle or the provision of medical care. For example, increasing the price of cigarettes may have as much an impact on reducing teenage smoking as billion dollar marketing campaigns designed to convince teenagers to not smoke (American Cancer Society 2004).

Modern medicine has developed an impressive array of pharmaceutical, nutritional, and surgical interventions, such as antibiotics, vitamins, and cardiac surgery. Because the environment can have such a profound affect on human health, it is important

to also develop environmental interventions to complement this array of medical interventions. Like medical interventions, environmental interventions make changes in structures, processes, or mechanisms in a person's environment in order achieve health. For example, lead abatement for a home is an intervention designed to promote the health of people living in that home.

Not all environmental interventions are local in scope. Interventions that are more general in scope might include removing asbestos from a school building, instituting a hygiene regimen in a hospital or regulating air pollution in a city. Environmental interventions that affect large groups of people can be defined as public health interventions. Since there is not a clear distinction between affecting individuals and affecting large groups (or populations) there is not a clear distinction between environmental interventions and public health interventions.[2]

Environmental health research can be defined as the systematic study of how the environment affects human health. This is a very broad category that includes many specialties and disciplines (Lavery et al 2003). Traditionally, the fields of epidemiology, occupational health, toxicology, ecology, and public health have focused on the relationship between the environment and human health (National Institute of Environmental Health Sciences 1996). Since almost all diseases have an environmental component, environmental health research now encompasses such fields as cardiology, oncology, gastroenterology, neurology, endocrinology, embryology, and pulmonology. For example, in understanding breast cancer, it is important to investigate all of the

different factors that may increase one's risk of contracting the disease, including genetic predispositions, diet, exercise, stress, and environmental exposures carcinogens, such as radiation or chemicals that cause cancer. If one understands how the environment affects breast cancer, one may able to make recommendations for changes in the environment designed to reduce the incidence of this disease, such as reducing exposure to carcinogens.

Environmental health research methods

There are a variety of different methods for studying the relationship between the environment and human health. Perhaps the most basic distinction is between methods that use an intervention to prove a connection between health and the environment and methods that do not (Sackett et al 2000). Interventional studies can be further divided into controlled and uncontrolled studies (Schaffner 2003). In a controlled study, a group of subjects, the experimental group, receives the intervention to be tested, while another group, the control group, does not. Controlled studies can be further divided into studies that use active controls and studies that use inactive controls (Emanuel and Miller 2001). In an active control trial, the control group receives an intervention that is known to be effective, while the experimental group receives a new intervention. In an inactive control trial, the control group receives an inactive treatment, or a placebo. The point of giving subjects a placebo is to control for bias related to the placebo effect in medicine. In a study that uses a placebo group as a control, the subjects and their caregivers will not know who is receiving the experimental treatment and who is receiving the placebo. The reason for instituting this double-blind (or "masked") method is that patients tend to

respond better to treatment if they (and their caregivers) believe that they are taking a treatment that works (Schaffner 2003).[3]

Controlled studies can be classified as randomized or non-randomized. A randomized study randomly assigns subjects to control groups and experimental groups to minimize biases that may affect the data. Randomization can reduce biases due to the preferences, beliefs, or attitudes of subjects or researchers. In a non-randomized, cohort study, researchers and subjects determine what types of intervention (or non-intervention) will be used (Sackett et al. 2000).

Non-interventional methods encompass a wide variety of research designs, including longitudinal studies of populations, such as prospective cohort studies; retrospective studies of populations, such as studies of cases and controls; review and analysis of databases, such as medical or public health records; review of biomedical literature, meta-analysis, case series, and case reports (Sackett et al 2000).

Some research methods are better than others for answering particular questions concerning the relationship between health and environment. Because it can demonstrate causation and minimizes bias, the randomized, controlled trial (or RCT) is generally recognized as the most reliable method for evaluating medical interventions (Sackett et al. 2000). The best RCTs also include groups that receive no intervention (or a placebo), since the use of this type of design minimizes the sample size needed to demonstrate a statistically significant effects. RCTs can help researchers demonstrate the effectiveness of health interventions (Emanuel and Miller 2001).

Although placebo-controlled, RCTs are recognized as the most reliable research method in biomedicine, there are ethical, legal, and practical reasons why researchers do not always use RCTs to answer medical questions. First, it may be unethical (or illegal) to conduct an intervention because the intervention would be too risky. The risks of any research study must be reasonable in relation to the benefits of the study to the subjects and society (Levine 1988; Emanuel, Wendler, and Grady 2000, Amdur 2003). Second, if there is already an effective intervention to treat or prevent a serious medical condition, then it may be unethical to use a placebo group as a control arm, since this would deny medical therapy to patients/subjects with a medical need. Withholding treatment is unethical, according to many, because it places the interests of the researchers ahead of the welfare of the subject (World Medical Association 2000), it places the researcher's obligation to advance medical knowledge ahead of the physician's obligation to treat the sick (Veatch 1987), or it exploits subjects for the sake of scientific research (Miller and Brody 2002).

When there is an effective therapy for a serious medical condition, subjects in the control group may be offered the established therapy. For example, studies on new blood pressure medications often compare new medications to current ones, since there are already effective therapies for hypertension. In some circumstances it may be appropriate to offer all of the subjects the new therapy, if the subjects have a life-threatening medical condition, the new therapy is expected to be effective, the results of the study will be clear and convincing and there is no other effective therapy (Schaffner 2003). In this type of

study, one can use the subjects as their own control group, comparing the subjects prior to receiving the new therapy and after receiving it (Schaffner 2003).

Finally, randomization may be impractical in some cases because subjects (or their representatives) do not want to consent to randomization, if, for example, they have a strong preference for one type of therapy (Levine 1988). It is widely recognized that it is unethical to randomize subjects to different groups without obtaining consent, except in some types of emergency research, where consent is not possible to obtain but the subjects may benefit from participation (Amdur 2003).

To summarize, although RCTs are widely recognized as the most reliable method for proving the efficacy of medical interventions, it may not always be ethical or practical to conduct RCTs to answer questions in environmental health research. Accordingly, environmental health studies frequently use other methodologies, such prospective (or retrospective) studies of cases and controls or review and analysis of databases. While this article will focus research that uses interventions, it is important to review the other methodologies that one might use in environmental health research, since it may not always be practical, legal, or ethical to conduct an RCT to determine the efficacy of an environmental intervention.

A hypothetical asthma study

To facilitate the discussion of ethical questions and problems that may arise in research on environmental interventions, it will be useful to describe a hypothetical study and explore some of the issues it raises.[4] We will not explore all the potential ethical

issues it raises in significant depth, but we will focus on those issues which pose some interesting and important questions for environmental health research.

Asthma is a serious health problem, affecting millions of people around the world. The rate of asthma among children and adults has increased dramatically in the last thirty years. In some countries, such as the United Kingdom, asthma affects 20% of the population. In the U.S., the incidence of asthma increased from 3.1% of the population diagnosed with the condition in 1980 to 5.4% in 1994 (Woodruff and Fahy 2001). Asthma accounts for a significant number of absences from work and school, physician offices visits, and hospital admissions (Mannino et al. 2002). Many different environmental exposures have been linked to asthma, including outdoor pollution, dust mites, insects, rodents, mold spores, pollens, pets, and allergens derived from other sources (Woodruff and Fahy 2001).

The purpose of this hypothetical study is to determine whether an allergen reduction method can reduce asthma symptoms and complications, such as missed work or school, hospitalizations, and use of medications. The study will recruit 80 families with children or adults, who already have asthma. Families who participate will be randomized to a control group of 40 families, who will receive no allergen reduction, or an experimental group of 40 families, who will receive the reduction. The allergen reduction method will include cleaning and decontamination of the house and the installation of a commercially available air purifier. These procedures are already used in many homes and have not been associated with any significant risk of harm, nor have they been

definitely shown to benefit people with asthma. The families in the control group will be asked to not undertake allergen reduction measures for asthma, although they may continue to receive medical care for asthma. Researchers have chosen to use an interventional methodology to test the effectiveness of the allergen reduction method because previous, non-interventional studies have provided some evidence suggesting that the reduction method is effective, but these studies have not offered any conclusive proof.

Researchers will collect data from the families related to asthma symptoms and complications and how these affect their quality of life. They also will collect and monitor data on the presence of allergens in the homes. The researchers will visit the homes four times during the study, to test for allergens in the homes. The families will complete quality of life surveys and record absences from school or work related to asthma, or other problems with participating in their normal activities. The families in both groups will be allowed to take their normal medications for asthma and have any necessary medical examinations or treatments for their asthma. The investigators will inform the families' physicians that they are taking part in this study. The study will last twelve months. All of the families will be paid $50 for each month that they participate in the study and will receive free literature on the causes of asthma and its prevention and treatment. The families in the allergen reduction group will receive free allergen reduction. The families may drop out of the study at any time.

A data and safety monitoring board (DSMB) will be established to review the data from the study and protect the health and safety of the subjects. All records will be kept confidential in accordance with federal regulations related to human research, including The Common Rule (2001) and the privacy rules set forth in the Health Information Portability and Accountability Act (HIPAA 1996). The study is jointly sponsored by a federal agency and a company that manufactures the air purifier. Six investigators are participating in the study. They are all employed by a large, research intensive university. The research team consists of a principal investigator with an MD and PhD, who is a full professor at the university; a junior investigator with a PhD, who is an assistant professor at the university, two post-doctoral students and two graduate students. Both professors on the team receive $2000 to $6000 per year for consulting with the company. All of the investigators have signed a confidential disclosure agreement (CDA) with the company, which gives the company the right to postpone publication of research results for as long as six months. The university, the company, and the government agency also have signed a Cooperative Research and Development Agreement (CRADA) to collaborate on this project, as well as a Material Transfer Agreement (MTA) pertaining to the transfer of data and research materials. The company could benefit from this research is the results are useful in marketing its air purifier.

Risk/benefit issues

This study poses some risks to the subjects, which must be reasonable in relation to the benefits of the study (The Common Rule; Emanuel, Wendler and Grady 2001).

Potential benefits to subjects may include health benefits, educational benefits, or psychological benefits, but not monetary benefits (Amdur 2003). Benefits to society may include new scientific discoveries and methods of diagnosing, treating, or preventing disease. All subjects in this study will receive some educational benefit from the free literature, and they may receive some psychological benefit if they derive satisfaction from participating in medical research. The subjects who are receiving allergen reduction also may receive some health benefits from the allergen reduction program. Since the efficacy of the program has not been proven, these benefits are only potential benefits. Society may benefit from the knowledge generated from this study if this information helps to develop new methods of treating or preventing asthma.

One might argue that the risks of the study are minimal. The Common Rule defines minimal risk as: "the probability and magnitude of the harm or discomfort anticipated in research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations of tests" (45 C.F.R. 46.102i). The allergen reduction procedures include cleaning and repair methods that are commonly used in homes. The most significant risk of these methods is accidental introduction of allergens, such mold, dust, or animal hair, or toxins, such cleaning fluids, into the home environment. These risks are no greater than the risks associated with professional cleaning services performed in homes. Although there may be some risks that cannot be anticipated, the risks of these procedures are probably very low. The subjects who did not receive the allergen reduction procedures

face the risk of living in a home for one year, with asthma, when the home requires allergen reduction. These risks may be more than minimal, depending on the status of their home environment. If the home has many different allergens and other factors that can cause asthma, then it may not be safe for the subjects to continue living in the unabated home.

To minimize these risks, researchers exclude families from participating if their home would not be safe to live in for one year without a proven allergen reduction method. Additionally, the researchers should continually monitor the health of subjects in the experimental and control groups to protect their health and safety. If it appears that the study is threatening the health of a subject living in one of the homes, then the researchers should ask that the home be withdrawn from the study, in order to protect the subject. The researchers may also decide not to enroll families if one or more family members have severe asthma. The researchers should also warn the subjects about serious health risks in the home that they discover during their investigation. For example, the researchers should inform the subjects if they discover dangerous levels of mold or improperly installed vents. The researchers may need to employ outside experts, such as air conditioning and heating contractors, to assist them in the inspection and assessment of the homes. Since the researchers are likely to find many health risks during their inspection, they will need to decide which ones would be considered serious enough to report to families, since there is no need to report all common, ordinary risks that one encounters in almost any dwelling.[5]

In addition to warning subjects about health hazards discovered during research, the researchers also have a duty to report illegal activities they are required specifically by law to report, such as child abuse/neglect, elder abuse/neglect, or domestic violence. Since the researchers will be examining subjects and spending a great deal of time in their subjects' homes, there is a significant chance that they will discover something that they are required by law to report. In this hypothetical study, researchers might discover that a child or adult is in desperate need of medical attention, and they may decide to notify the appropriate authorities, such as the local department of social services, about this problem. The researchers should understand the local reporting laws prior to undertaking this hypothetical study, and they should discuss these requirements with potential subjects prior to enrollment.

To summarize this section, the risks of this study appear to be reasonable in relation to the benefits, provided that steps are taken to minimize these risks, such as carefully designed inclusion/exclusion criteria, monitoring subjects, and informing subjects about potential health risks discovered during the study. To obtain a better estimate of risks, it is important to get more information pertaining to the risks of the allergen reduction program and the risks of living of an asthma patient in an unabated home for one year. The Institutional Review Board (IRB) overseeing this research study may decide to solicit the help of an outside expert to assist in that assessment.

The control group

This hypothetical study will use a control group that receives no allergen reduction to determine whether the allergen reduction procedures are effective.[7] It also will randomly assign families to different groups. As discussed earlier, this method is a reliable way of testing hypotheses concerning interventions designed to treat or prevent disease. Withholding effective interventions from subjects is one the most controversial ethical issues in clinical research. While there is general agreement concerning that withholding available, effective therapies in biomedical research is morally problematic and unsupportable in practice, there has been a great deal of debate about what it means for a treatment to be effective and available to participants. This article will briefly review these issues, since they have some implications for environmental health research.

Most researchers and ethicists agree that it is acceptable to withhold an experimental therapy if there is no commonly accepted, effective therapy prior to beginning a study (Freedman 1987). Once a therapy is determined to be effective, however, researchers have an obligation to stop the study and offer the therapy to subjects in the control group (Emanuel and Miller 2001).[6] Since the experimental therapy may have its own risks, subjects in the experimental group may be exposed to a greater risk of harm than subjects in the control group, and the “lucky” subjects may be those in the control group (Levine 1988). If researchers determine that an experimental therapy poses undue risks to participants, they have an obligation stop administering that therapy to the participants.

How do the above considerations apply to research on environmental health interventions? To answer this question, one must consider in what ways an environmental health intervention may be similar to medical therapy. On the one hand, one might argue that an environmental intervention is like therapy because an environmental intervention can help to diagnose, treat, or prevent a medical condition. To return to our hypothetical case, suppose that researchers have evidence that an allergen reduction program can reduce hospitalizations for asthma by 20% and reduce the number of days of school or work missed by 30%. Denying this allergen reduction program to a person with asthma would be like denying a medication that has similar beneficial effects. In either case, one would be withholding a known health benefit from a person. It does not make any significant difference whether a person benefits from medication prescribed by a physician or lives in a better environment. Thus, withholding an effective environmental intervention would be comparable to withholding asthma medication.

On the other hand, one might argue that the relationship between patients with asthma and physicians who prescribe drugs for asthma is very different from the relationship between a person with asthma and someone who performs and studies allergen reduction procedures on her home. In the first instance, the two people have a physician-patient relationship; in the later, they do not. The physician-patient relationship is a well-established social arrangement. Physicians are licensed professionals entrusted by patients and society to exercise good judgment, abide by legal and ethical duties, and maintain competence and expertise (Wynia et al 1999). One might argue that the

relationship between a researcher and a subject is more like that between two contracting adults than between physician and patient. Contracting parties do not have duties to benefit each other, unless these duties are spelled out in the contract. The researchers only have those duties that are set forth in their contractual arrangement and expressed, for example, in the informed consent document. If the subjects consent to participate in a study in which they will not receive allergen reduction, then their agreement is legally binding and ethical. Thus, the researchers have no special duty to benefit their subjects or protect them from harm, unless, of course, they also happen to be the subjects' health care providers.

The problem with this argument is that the relationship between a person with asthma and someone who studies how the environment affects asthma in that person is more than a mere contractual relationship (Resnik, 2004a). The relationship between research subject and researcher, even in a non-medical context, is still defined by mutual trust and partnership (Veatch 1987). Even though non-physician researchers do not have an obligation to benefit research subjects that is similar to the obligation a physician has to benefit his or her patient, they still have duties to respect the rights of research subjects and protect them from harm and exploitation (National Commission 1979, Miller and Brody 2002). If the allergen reduction procedures in this hypothetical study are known to be effective and available to subject, for example, then the researchers should not use an inactive control group. They could, however, use active control groups, such as groups with different degrees or types of allergen reduction. Furthermore, if they are using an

inactive control group at the beginning of the study, and an abatement procedure is proven to be effective during the course of the study, then they should stop the study and offer the abatement procedure to all subjects.

Assuming that it is unethical to withhold environmental interventions that are known to be effective from research subjects, the next question to ask is how one knows that an environmental health intervention is effective. What counts as adequate proof of the effectiveness of an environmental intervention? In thinking about this question, it will be useful to distinguish between different types of proof (Miller and Weijer 2003):

a) Non-professional acceptance, such as commercial success or widespread use of an intervention;
b) Professional acceptance, such as acceptance and use of an intervention by people with appropriate training, experience, and expertise;
c) Scientific evidence, such as data from systematic studies, such as RCTs or prospective cohort studies.

Most people would agree that non-professional acceptance is not sufficient proof of acceptance. Many types of non-standard medical therapy have been successfully marketed and sold for years, but this is only the most limited evidence that these therapies work. Before the professionalism movement in medicine, many people without any training or experience sold quack "cures," such as snake oil (Porter 1999). Even today, consumers willingly spend billions of dollars per year on unproven therapies, such a homeopathy and herbal medicine (Eisenberg et al. 1998). Professional acceptance, while

important, is also not sufficient proof that an intervention is effective. Professionals may decide to accept treatments based methods that are highly susceptible to bias, such as tradition, personal preference, and anecdotal evidence (Sackett et al. 2000). Healthcare interventions should be regarded as effective only when they have been subjected to scientific tests and evaluations.

If an intervention should be regarded as effective only if it is supported by scientific evidence, then one may conduct studies that use inactive controls to assess the intervention if there is no scientific evidence supporting the intervention. Applying this conclusion to the hypothetical allergen reduction study, it would be ethical to use an inactive control group in this study, provided that there is no sound scientific evidence demonstrating the effectiveness of the intervention (the air purifier and cleaning) at the outset of the study. This would still be the case even if some allergen reduction procedures have achieved a high degree of commercial success or acceptance among professionals. As long as there is no scientific evidence in favor of the effectiveness of such procedures, it would not matter that they meet these other standards of "proof." What matters is scientific proof, not widespread, commercial success, or popularity among professionals. Indeed, biomedical researchers have an obligation to scientifically evaluate popular interventions that have not been tested. For example, researchers should apply scientific methods to complementary and alternative medicine (Angell and Kassirer 1998).

Questions about the "availability" of effective treatments arose in controversies concerning HIV research in developing nations (Resnik 1998). In this dispute, researchers

used a placebo group to test the effectiveness of different dosing regimens of AZT in the prevention of mother to child (perinatal) HIV transmission. When this study begin, a drug regimen known as the 076 protocol had been proven effective in studies on populations in the developed world. Since the 076 protocol used about $1000 worth of AZT, very few patients in the developing world had access to this treatment, since most developing nations spend less than $400 per capita on health care. One of the goals of the study was to develop an effective method for preventing perinatal HIV transmission that people in developing nations could afford. Critics of the study argued that it was unethical because it withheld an effective treatment from research subjects (Lurie and Wolfe 1997). Defenders of the study countered that the research subjects did not have access to any medical treatment, so they were not being denied a benefit that they would have had otherwise, because effective treatments were not available in the developing world. Physicians participating in the study did not violate their duty to treat patients because they did not have access to any medications to prevent perinatal transmission of HIV. The subjects were not harmed by the study because they were not made worse off than they otherwise would have been (Varmus and Satcher 1997).

The issue of using placebo controls groups in research conducted in the developing world continues to generate a great deal of debate, and prompted the World Medical Association to revise its Helsinki Declaration. According to the latest version of these important ethical guidelines:

> The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic or therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (World Medical Association 2000).

These guidelines imply that it would be unethical to use an inactive control group to test an environmental health intervention in a developing nation, if an intervention has already been proven to be effective in a developed nation. The Council for the International Organization of Medical Sciences (CIOMS) also recently revised its guidelines for international research involving human subjects. The CIOMS guidelines are not as strict of the Helsinki Declaration:

> As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment". Placebo may be used: when there is no established effective intervention; when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; when use of an established effective intervention as comparator would not yield scientifically reliable results

and use of placebo would not add any risk of serious or irreversible harm to the subjects (CIOMS 2002).

The CIOMS guidelines create three exceptions to the prohibition against inactive controls: (a) when there is no proven effective intervention (which we have already discussed); (b) when withholding an effective intervention would produce only a delay in relief of symptoms; and (c) when using an effective intervention as a control would not yield scientifically reliable results and would not add any risk of serious or irreversible harm to subjects. Although these last two exceptions are important, they do not create a very large window for research with placebos once an intervention is proven to be effective. Basically, these last two exceptions allow for the use of placebos only when there is no risk of serious or irreversible harm to subjects.

We will not attempt to resolve all these issues concerning inactive controls here, but we will explain how they might pertain to environmental health research. Suppose the abatement procedures in the hypothetical asthma study are proven to be safe and effective in a study in the developed world. If this is the case, then one might argue that it would be unethical to use an inactive control for a study conducted in the developing world. One could compare different types of allergen reduction, but one could not compare abatement and no abatement, since this would be denying an effective treatment to research subjects. The Helsinki Declaration would recommend this approach. The CIOMS guidelines would allow researchers to use an inactive control only if denying allergen reduction would produce no serious risk of irreversible harm to subjects. So, the important question

researchers would need to face when designing a study that uses an inactive control when an effective intervention exists would be, "will denying subjects the effective intervention result in long-term serious or irreversible harm?" If the answer to this question is unquestionably yes, then researchers should not use an inactive control. If the answer to this question is "maybe," then researchers may consider using an inactive control only for a compelling moral reason, such as the need to deal with an urgent public health threat, like the HIV/AIDS pandemic (Resnik 1998).

Subject selection

Ethical guidelines and research regulations require that the selection of subjects is equitable (Emanuel, Wendler and Grady 2000). This rule implies that inclusion and exclusion criteria should be crafted to meet two (often conflicting) goals: (1) protection of vulnerable subjects from potential harm or exploitation; and (2) fair distribution of the benefits and burdens of research. The National Commission (1979) was especially concerned about egregious episodes of exploitation of vulnerable subjects, such as the Tuskegee syphilis study and the Willowbrook hepatitis experiments. The Commission recommended that vulnerable subjects, i.e. subjects who are not able to consent to research or promote their own interests, should be protected against involvement in research solely for administrative convenience. This recommendation led to the development of a variety of federal regulations that mandate extra protections for children, prisoners, fetuses and embryos, and pregnant women (McCarthy 1998). While there are no federal regulations that deal specifically with mentally disabled subjects, various

organizations, such as the National Bioethics Advisory Commission (NBAC), have made recommendations for extra protections for these subjects (Shamoo and Resnik 2003).[8]

Prior to the 1990s, equitable subject selection was equated with protecting vulnerable subjects from research risks. For this, as well as other reasons, women, minorities, and children were routinely excluded from clinical research.[9] The political landscape changed in the 1990s. Justice in research no longer meant exclusion from medical research but inclusion in medical research. Feminists and women's health advocates demanded greater access for women to the benefits of medical research, including inclusion in clinical trials. They argued, convincingly, that policies designed to protect fetuses and women from harm had an adverse impact on women's health (Dresser 2001). Soon minorities made similar arguments to demand greater access to medical research, and government polices changed in response to this political pressure (Dresser 2001). The National Institutes of Health (NIH) and the Centers for Disease Control (CDC) both developed policies requiring researchers to include women and minorities in research, unless inclusion threatens the health of the subject or is inappropriate, given the goals of research (NIH 1994, CDC 1995). By the end of the decade, pediatricians and children's health advocates argued that children were not adequately represented in medical research (Nelson 1998). Many drugs that physicians prescribe for children have not been tested on children. Although the Food and Drug Administration (FDA) has approved these drugs to treat adult medical problems, physicians often prescribe them to

children on an "off-label" basis (Kopelman 2000). To encourage companies to sponsor studies related to children's health, Congress has passed legislation granting six months of additional patent protection for drugs that have been tested on pediatric populations (Tauer 1999).

Today, equitable subject selection involves a careful balancing of the goal of protecting vulnerable subjects from harm and the goal of including women, minorities, children and other underrepresented groups in research. Research studies include extra protections for vulnerable subjects as well as measures designed to encourage inclusion of different groups, unless exclusion of a particular group is scientifically or ethically appropriate.

How might this approach to subject selection apply to the hypothetical allergen reduction study? First, equitable subject selection requires that researchers take steps to protect vulnerable subjects from harm. These subjects might include children, pregnant women, and mentally disabled people. For the sake of this example, we shall assume that none of the families would include any subjects that would be classified as prisoners. There are three basic strategies that have been used to protect vulnerable subjects: (1) representation by someone familiar with the needs and concerns of the vulnerable group on the Institutional Review Board (IRB) or other comparable committee that reviews research on human subjects; (2) extra safeguards for obtaining consent, such as consent by a legally authorized representative and, if appropriate, the subject's assent; and (3) restrictions on the types of risk that vulnerable subjects may face in research (Shamoo and

Resnik 2003). Applying these concepts to the hypothetical study, it would be important for the IRB to have adequate representation to address the needs and concerns of vulnerable groups, if these groups are to be included in the study (Amdur 2003). Since it is likely that the study would include families with children, pregnant women, the IRB should include members who are capable of speaking to the needs and concerns of these groups. The study also should develop an informed consent document that can be signed by a legally authorized representative as a well as an assent form for minors of appropriate age.

What about risks? This is a complex issue that involves different federal regulations for different classes of subjects. For the sake of simplicity, we will focus only on the regulations pertaining to the risks that children may encounter in the study. The basic philosophy expressed in the federal regulations is one of protection: children should be protected from more than minimal risks in research, unless they stand to benefit from the research or the research is vitally important for pediatric health, in which case additional requirements must be met. The federal regulations for research on children (45 C.F.R. 46.401-409) classify research studies according to the risks and benefits for the subjects and distinguish between four distinct categories of research on children that are permissible:

1. Research involving no more than minimal risk (45 C.F.R. 46.404), where 'minimal risk' is defined as "the probability and magnitude of harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily

encountered in daily life or during the performance of routine physical or psychological exams or tests" (45 C.F.R. 46.1029(i).)

2. Greater than minimal risk research with the prospect for direct medical benefit to the child (45 C.F.R. 46.405). Risks must be reasonable in relation to the potential benefits.
3. Minor increase over minimal risk research, with no prospect for direct medical benefit to the child, but with the prospect of knowledge important for understanding or ameliorating the subject's condition, which uses procedures that are similar to their actual or expected experiences (45 C.F.R. 46.406).
4. More than minimal risk research, not otherwise approvable in categories 1-3, which present an opportunity to understand, prevent or alleviate a serious pediatric health problem (45 C.F.R. 46.407). This type of research requires the approval of the Secretary of the Department of Health and Human Subjects.

To determine how these regulations apply to the hypothetical asthma study, one must first assign a degree of risk to the research. Is the research minimal risk or more than minimal risk? In assessing this degree of risk, it is important to focus on the risks related to the research methods or procedures, not on the risks related to the subject's underlying health problem (Amdur 2003). For example, a survey of chemotherapy patients' attitudes toward death and dying is the risk of the survey, not the risk of the chemotherapy, since the survey, not the chemotherapy, is the research method or procedure being used to gather data. In the Grimes case, the Maryland Courts of Appeals included the risks of the

subjects' environment in its assessment of risks. The court opined that the risks of the experiments were the risks associated with living in a home that had dangerous level of lead, not merely the risks taking dust and blood samples (Hoffman and Rothenberg 2002). We agree with the Maryland court's approach to assessing risks in environmental health research, since the exposure to a particular environment is part of the research method. Thus, in assessing the risks of this hypothetical allergen reduction study, one must consider the risks of procedures used to test and monitor homes, the risks of receiving allergen reduction, as well as the risks of living in a home that does not receive allergen reduction.

Taking all of these risks into account, one may ask, "Does the experimental group or the control group encounter risks that are more than minimal?" This question is impossible to answer without taking a closer look at the proposed abatement methods. As noted earlier, the IRB may ask for some expert opinion and advice on this issue, if it lacks the knowledge or expertise to assess the risks of the proposed research methods. Since the proposed methods are procedures that are already being used in homes, it is likely that these methods pose only a minimal risk to subjects but the risk may be more than minimal. Concerning the subjects in the control group, they face the risk of continuing to live in an environment that has not received allergen reduction. Since the subjects are currently living in an unabated home and can still receive medical treatment for their asthma, the research is not exposing them to any risks beyond those that most people ordinarily encounter in daily life, since most people live in homes that have not received allergen

reduction. Thus, only the experimental group encounters risks that may be more than minimal.

Suppose that the risks encountered by the experimental group are more than minimal, could the research still be justified because it offers direct medical benefits to the subjects? The answer to this question should be "yes." Even though allergen reduction may not be classified as medical treatment or therapy, we shall assume that it has the prospect of directly benefiting the health of people with asthma. Indeed, the purpose of the research is to assess the efficacy of allergen reduction methods. Presumably, the researchers have some preliminary evidence that leads them to believe that these procedures may be effective. Once again, answering this question requires additional expertise that the IRB may lack, and the committee may need to solicit the opinion of an outside expert. Even if the IRB determines that the research does not offer direct, medical benefits to the children, it could still help with understanding or ameliorating the condition of the subjects with asthma and would probably only involve a minor increase over minimal risk. Thus, the research might still be approved under the third category of pediatric research.

To summarize, the asthma study would probably be permitted as minimal risk research. If the study is classified as more than minimal risk, it could be approved as research that offers direct, medical benefits to the pediatric subjects. If, by some chance, the IRB determines that the research does not offer direct medical benefits to the subjects, it could be approved as research that helps to ameliorate or understand their condition.[10]

Assuming the study has adequate provisions to protect vulnerable subjects from harm, one must ask whether it would be appropriate to exclude any groups of subjects for scientific or ethical reasons (such as protection from harm). One could argue that since the study has such a low degree of risk, there are probably no good ethical reasons to exclude any groups of subjects who might be adversely affected by the study, except, perhaps, subjects with severe asthma, who might be excluded for their own safety and protection. Since asthma strikes males and females of different races, ethnicities, ages, and social classes, there are probably no good scientific reasons to exclude groups of subjects as well. On the contrary, there are both scientific and ethical reasons to make an effort to recruit a study population with demographics similar to those one finds in the population of asthma patients. The researchers should make a concerted effort to recruit children, women, minorities and other underrepresented groups. Appropriate recruiting techniques could include advertising, focus groups or town meetings, and a nominal payment for participation.

Privacy

Ethical guidelines, federal research regulations and the Health Information Portability and Accountability Act (HIPAA) require biomedical researchers to protect the privacy and confidentiality of research subjects (Amdur 2003). Researchers should take steps to promote the security and integrity of research records, and control access to the records. The federal research regulations also require researchers to discuss confidentiality and privacy during the consent process. It can be difficult to protect

privacy and confidentiality in research on environmental health interventions, since this research often takes place in the home or at work. It may be difficult to prevent people from discovering that research is taking place at a particular location. In the hypothetical asthma study, neighbors may discover that a particular family is receiving allergen reduction as part of a research study. To guard against this breech of privacy, researchers should be discrete. When entering homes, they should not call attention to themselves. They should answer questions in the home, not out in the street. They should drive a vehicle that would not be identified as belonging to a research study, and they should wear clothes that do not look like clothes warn by researchers. Researchers should also consider obtaining a Certificate of Confidentiality from the federal government, which will help to provide protections for the privacy of research data. For example, a Certificate of Confidentiality can prevent outside parties from using a subpoena to obtain access to private informed contained in research records.

Informed consent

Federal regulations and ethical guidelines also require researchers to obtain informed consent from research subjects or their legally authorized representatives. Informed consent is more than signing a document: it is a conversation between researcher and research subject (Emanuel, Wendler and Grady 2000). The process of informed consent should include a discussion of the purpose of the research; the research procedures and methods; benefits and risks of the research; alternatives; measures taken to protect confidentiality; costs and payments (if any); compensation for injury (if relevant);

potential termination of the subjects participation by the researcher; the number of subjects in the study; the right to withdraw from the study without penalty; notification of new findings that may affect the subject's decision to participate in the study, and whom to contact for more information or questions (Amdur 2003). Researchers in the hypothetical asthma study, as well as other researchers studying environmental interventions, should discuss all of these topics. As mentioned earlier, the researchers should also inform the subjects of plans to monitor the health of the subjects and to warn them about hazards that are discovered during the research. Researchers should also inform the subjects that they are required by law to report some activities that threaten the health and safety of subjects, such as child abuse/neglect.[11]

Because the study will involve research on families in their homes, it raises the question, "who will be asked to consent?" Since ethical and legal rules require that subjects (or their legal representatives) consent to research, with some specific exceptions, to determine who should give consent, one needs to first determine who will be a research subject. A research subject, according to the U.S. federal regulations is a living human being, which researchers collect data about through an intervention with the subject or by gathering private information about the subject (45 C.F.R. 46.102(f)). The researcher should obtain proper consent from anybody in the home environment on whom they collect data. In this study, the researchers plan to gather data on the entire family, so all family members must provide consent. The researchers do not have to obtain consent from people who happen to be in the home but are not research subjects, such as visitors

or guests. If there are adults in the family, they can consent for their own participation. If there are children in the family, then their legal representatives, such as their parents, can provide consent. If appropriate, the children may also sign an assent form. If the researchers decide that they do not need to include all the family members in the study and decide to focus only on those family members with asthma, then they change their protocol to reflect this shift in focus. If the study only collects data on family members with asthma, then only these subjects (or their representatives) need to provide consent.

The researchers should be prepared to deal with the possibility that family members may not all agree to participate in the study. Suppose a family has a mother, a father, and two children and the mother wants to include herself and her two children in the study, but the father does not want to be in the study. The father clearly has the right to not participate, but how would his decision affect the other people in the family? Although the federal regulations do not provide consent of both parents for this type of research (see 45 C.F.R. 46.408(b)), the father would still have the legal authority to prevent his children from participating, assuming that he has full custody rights. While the father would not be able to prevent the mother participating, enrolling only the mother but not the father or the children could bias the results, especially if the mother does not have asthma. Thus, researchers should consider excluding an entire family from a study if they have difficulty obtaining consent from each member (or legal representative).

Conflict of Interest

Since two of the investigators are receiving compensation for consulting with the company that is sponsoring the research, there are some potential conflicts of interest related to this study. A conflict of interest (COI) in research is a situation where the researcher's financial, personal or professional interests are likely to affect his or her judgment (Resnik and Shamoo 2003). As a result, the researcher may make biased scientific decisions or fail adhere to his or her ethical or legal obligations. An apparent COI in research is a situation where a reasonable, outside observer would conclude that the researcher's judgment has been affected by his or her financial interests. It is important for researchers to deal with COIs and apparent COIs because these situations can undermine the integrity and trustworthiness of research. There are three basic strategies for responding to COIs: disclosure, conflict management, and conflict avoidance (or prohibition). Ideally, researchers should disclose all COIs and apparent COIs and avoid COIs that pose a serious threat to the integrity and trustworthiness of research (Resnik and Shamoo 2003).

In this study, the researchers should disclose their financial interests to the IRB and to the research subjects. Disclosing this information will allow the IRB to decide whether these interests pose any risks to human subjects that require additional monitoring or oversight. Disclosing the information to the subjects will allow them to decide the interests might have an affect on the integrity or trustworthiness of the researchers, which could affect their decision to participate in the study (Resnik 2004a). Disclosure should be an adequate response to these COIs, since the money at stake—$2000-$6000—is not

very great, judged against professional standards for compensation. If the researchers were receiving much more money, or had a leadership position or stock in the company, then other measures might be appropriate, such as conflict management or prohibition (Morin et al 2002).

Community-Level Issues

In addition to the foregoing considerations regarding the rights and welfare of individual research subjects, studies of environmental-health interventions often raise ethical challenges regarding researcher relationships with the communities in which a research study is done (Lavery et al 2003). The choice to study a purported environmental hazard, for example, may suggest to members of the community that the particular hazard under investigation is an especially important determinant of public health (Sharp 2003). The choice to study a particular environmental hazard also may selectively empower some members of a community and not others. In our hypothetical asthma study, there may be members of the community who lobby for increased public attention to improving air quality. Those persons in the community may gain more political prominence within the community or become more visible spokespersons on behalf of these issues as a result of their association with a research study. Activists might also use specific research findings to serve particular social or political agendas. These possibilities suggest that when environmental-health researchers initiate an interventional project they should be mindful of the possibility that their work may significantly affect the internal social dynamics of a community, often in ways that may be difficult to anticipate in advance.

Since research can influence community dynamics in ways that are difficult to predict, many public-health researchers support the active participation of members of the community in the design, development, and implementation of public-health research.[12] Advocates of this approach, often described as community-based participatory research (CBPR), stress several potential benefits of more active community partnerships with public-health researchers (Minkler et al 2003). For example, involving members of the community in the development of research hypotheses may help make research findings more directly relevant to the interests of the community; involving members of the community in the development of recruitment strategies and informed-consent procedures might also help researchers identify potential risks to subjects and other members of the community that might otherwise go unnoticed; and involving members of the community at various stages of research recognizes both the local knowledge possessed by members of the community and the importance of treating lay partners in research with a level of respect they are deserve (Sharp and Foster 2000). Moreover, failing to involve the community substantively in the development of an interventional public-health study may signify to some members of the community arrogance on behalf of the researchers or a purely instrumental interest in the community's health.

Other issues

Every research study raises a variety of ethical and scientific issues that we cannot discuss fully here. A more complete discussion would also address the following: subject payment; recruitment; advertising; statistical justifications for the sample size, such as

power analysis; compensation for injury; communication of results to the public; and data and safety monitoring. We do not include a discussion of these issues, because they have been addressed elsewhere in the literature.

Conclusion

Some writers have expressed the concern that the opinion in *Grimes* could have a chilling effect on environmental health research (Hoffman and Rothenberg 2002). We hope that this is not the case. Environmental health research, especially research on environmental interventions, is a very important part of our understanding of human health and disease. The Grimes case provides researchers and ethicists with an opportunity to clarify and strengthen some of the ethical and legal obligations that arise in environmental health research on human subjects, and we have tried to contribute toward that goal in this article. We hope that other writers expand this discussion and explore these issues in more depth. Research on environmental interventions on human subjects can and should go forward, provided research studies meet prevailing scientific, ethical, and ethical standards.[13]

Notes

[1] The goal of the KKI study was to assess the effectiveness of different forms of lead abatement. KKI researchers enrolled 25 low-income families in the study and divided them into five different groups. Three of the groups included families living in houses where lead paint was known to be present. These three groups were randomly assigned to receive varying degrees of repair and maintenance to reduce exposure to lead. The study

also included a group of families living in houses that had already undergone complete lead abatement, and a group of families living in houses that never had been painted with lead paint. The KKI study collected dust samples from these houses and measured lead levels in the blood of children living with those families to determine the effectiveness of lead abatement programs. Prior to recruiting families to participate in the study, KKI researchers reached agreements with landlords to allow their building to be part of the study, encouraged the landlords to rent to families with young children, and helped the landlords obtain grants to pay for lead abatement (*Grimes vs. Kennedy Krieger Institute, Inc.* 2001). When the study began, the landlords were not required by law to reduce lead exposure in their buildings. Young children exposed to environmental lead are at risk for lead poisoning and permanent brain damage (Hoffman and Rothenberg 2002). The plaintiffs sued KKI and several researchers, arguing that they did not receive adequate informed consent about the research and were not warned about dangerous lead levels in a timely fashion. The defendants moved to dismiss the case on the grounds that they did not have any legal duties to the plaintiffs that could serve as a basis for a lawsuit. The circuit court ruled in favor of the defendants, and the plaintiffs appealed this decision. The Maryland Courts of Appeals ruled in favor of the plaintiffs and remanded the case back to the lower court. The Court of Appeals said that the researchers had a legal duty to the subjects, based on the federal research regulations and the informed consent document. The Court also engaged in a lengthy discussion of the duties that researchers owe subjects in non-therapeutic research (*Grimes vs. Kennedy Krieger Institute, Inc.* 2001). The court

found that a parent or guardian may not give consent for a child's participation in non-therapeutic research in which the subject faces any risk of damage or injury. KKI, as well as several other organizations that support biomedical research, asked the court to reconsider its ruling, on the grounds that the opinion could undermine pediatric research and was more restrictive than the federal regulations on pediatric research, which allow children to participate non-therapeutic research that constitutes only a minimal risk to subjects. While the court did not change its ruling, it clarified its opinion and stated that children can participate in non-therapeutic research if the research poses only a minimal risk to the subjects (Nelson 2002). Non-therapeutic research is research in which the subject has no prospect of a direct health benefit. Most commentators hold that it is morally acceptable to expose children to more than minimal risks in therapeutic research if the subjects can benefit from the research. For example, a child with cancer may participate in a study of a new cancer drug, if participation in the study offers the child medical benefits. Since the Maryland Court of Appeals focused on questions relating to Maryland's law, the implications of *Grimes* for other courts and cases are unclear. While Maryland district courts are obligated to follow *Grimes*, other state or federal courts could reach different conclusions. Even so, it is likely that other courts will examine *Grimes* to consider its legal reasoning and insight (Resnik 2004b).

[2] Biologists often speak of various types of environments, such as the intracellular environment or the extracellular environment. The best way to understand this usage of the word 'environment' is to regard the environment as a relational concept in

biomedicine. One could view an organism as an environment relative to a cell within the organism; a cell as an environment relative to one of its organelles, such as the nucleus, and so on (Brandon, 1995). Indeed, it makes sense to say that there is not one environment but that there are many different types of environments at different levels of biological organization (Eldredge 1985). Thus, the line between environmental interventions and pharmaceutical, surgical or dietary interventions may also be blurry. For the sake of clarity, this article will focus only on those interventions occurring at the organismic level of organization, not on those occurring at lower levels.

[3] Some researchers have recently challenged the significance of the placebo effect in biomedicine, see Hrobjartsson and Gotzsche 2001.

[4] This hypothetical case is similar to several real cases, such as Morgan et al (2004). We are using a hypothetical case in this article because we want to focus on the ethical issues at stake in environmental interventions and we are not interested in criticizing any particular research study. In this case, we refer to the people who are being studied as "subjects." We are aware that some writers prefer to use the term "participants," but we have chosen not to use this term because we think that it can obscure the fact that people who are being studied are often vulnerable and easily manipulated. Moreover, the federal regulations and other important legal documents use the term "subject."

[5] It is worth noting that the duty to warn was an important issue in *Grimes* (Hoffman and Rothenberg 2002). The plaintiffs alleged that the defendants failed to fulfill their duty to warn them about dangerous lead hazards in their homes in a timely fashion. During the

study, the researchers from KKI collected data on lead dust in the homes, but they allegedly failed to notify subjects about these risks in a reasonable time (*Grimes v. Kennedy Krieger Institute, Inc*. 2001). One of the plaintiffs in Grimes, Catina Higgins, claimed that her son, Myron, suffered a learning disability, shortened attention span, reading difficulty, and hyperactivity as a result of KKI's failure to inform her in a timely fashion about dangerous lead levels in the home and in her son's blood (Hoffman and Rotherberg 2002). One important lesson that environmental health researchers should learn from *Grimes* is that they have a duty to warn subjects about health risks in the environment that they discover during the course of their research. Researchers undertake this duty because the relationship between researcher and subject is a fiduciary one: researchers are entrusted with protecting the health and safety of research subjects (Veatch 1987). In U.S. law, a fiduciary relationship is defined as "a relationship in which one person is under a duty to act for the benefit of the other on matters within the scope of the relationship (*Black's Law Dictionary* 1999). In an important research ethics case, the California Supreme Court found that medical researchers have fiduciary duties to their subjects/patients (*Moore v. Regents of the University of California* 1990). In this case, the researchers had patented a cell-line that they had taken from Moore following an operation to remove his spleen. The plaintiff, Moore, argued that the researchers breached their fiduciary duties by failing to inform him about their financial interests related to their relationship. However, a recent case found that researchers do not have a fiduciary relationship with their subjects in non-therapeutic research (*Greenberg v. Miami*

Children's Hospital 2003). In this case, the subjects alleged that the researchers breached their fiduciary duties by failing to inform them about their financial interests in patenting a genetic test. The court said that the researchers did not have fiduciary duties to their subjects because they only collected tissue from their subjects and did not have a therapeutic relationship with their subjects. The court held that therapeutic research gives rise to fiduciary obligations but not non-therapeutic research. It remains to be seen whether other courts follow the court's opinion in Greenberg, but many ethicists have argued that the therapeutic vs. non-therapeutic distinction lacks merit (Levine 1988). Federal research rules and guidelines, such as The Common Rule (1991) and The Belmont Report (National Commission 1979) do not make such a distinction.

[6] There is a large body of literature on clinical equipoise in medicine and stopping rules. The controversy focuses on epistemological questions concerning the evidence one needs to start or stop a study, and who makes these decision. See Miller and Weijer (2003) and Miller and Brody (2002) for a review.

[7] The problems we discuss here would be as pronounced if the hypothetical study used a cross-over method. In a cross-over study, one switches the intervention and experimental groups halfway through the study. Although cross-over studies can allow more subjects to benefit from access to experimental therapies, they can also be difficult to interpret because the control group in the second half of the study has already been exposed to the intervention.

[8] The adjective ‘vulnerable’ has been applied many others subjects besides those that are protected by specific regulations, including gravely ill patients, students, impoverished patients, and patients who do not speak the language of the country in which research is conducted. For further discussion, see Macklin (2003).

[9] Women, minorities and children have also been excluded from research for practical and economic reasons. Minority patients, especially African Americans, tend to have a low level of trust in the biomedical research establishment, due to their awareness of episodes of exploitation and abuse, such as the Tuskegee study. Consequently, researchers often have difficulty recruiting patients from racial or ethnic minorities (Dresser 2001). Pharmaceutical and biotechnology companies make research funding decisions based on profit potential. Many of these firms have decided that more profit can be gleaned from studying problems that affect rich, white men than from studying problems that affect children, minorities, or poor people (Resnik 2001).

[10] One might argue that the researchers in the KKI study did not violate the federal regulations for pediatric research. While the KKI study was probably a more than minimal risk study, it also probably resulted in direct medical benefits to children, since there were no inactive control groups in the study. All of the children lived in houses that received some type of lead abatement. If the study had recruited families and required them to live in unabated houses, then this would have exposed children to more than minimal risks with no medical benefits. Critics of the KKI study, including the Maryland Court of Appeals, have argued that researchers should not have exposed children to such

high levels of risk in non-therapeutic research. This argument misses the point: the federal regulations do not distinguish between therapeutic and non-therapeutic research. What matters is whether children are expected to receive direct, medical benefits.

[11] The plaintiffs in *Grimes* alleged that they were not adequately informed about the risks of living in a home with dangerous lead levels.

[12] Involvement of community in research can introduce bias into the study, since community members may want the results of the research to promote their interests. Although researchers should be mindful and this potential bias and should takes step to minimize it, this concern is not a sufficient reason for refusing to involve community members in research.

[13] The International Society for the Study of Environmental Epidemiology (ISEE) has developed ethics guidelines for research (ISEE 1999; Sokolne and Light 1996). Our paper reinforces many of the important insights contained in the ISEE's pioneering work.

Acknowledgements

We would like to thank Ernest Kraybill, Walter Rogan and two anonymous reviewers for helpful comments.

References

Amdur, R. (2003). *Institutional Review Board Member Handbook.* Boston: Jones and Bartlett.

American Cancer Society. (2004). How to fight teenage smoking. Available at: http://www.cancer.org/docroot/PED/content/PED_10_14_How_to_Fight_Teen_Smoking.asp. Accessed: August 17, 2004.

Angell, M. and Kassirer, D. (1998). Alternative medicine—the risks of untested and unregulated remedies. *New England Journal of Medicine* 339: 839-41.

Black's Law Dictionary (7th ed.). (1999). St. Paul, MN: West Group.

Brandon, R. (1995). *Adaptation and Environment*. Princeton, NJ: Princeton University Press.

Collins, F. and McKusick, V. (2001). Implications of the Human Genome Project for medical science. *Journal of the American Medical Association* 285:540-44.

Collins, F. (2004). The case for a US prospective cohort study of genes and environment. *Nature* 429:475-77.

Council of International Organization of Medical Sciences (CIOMS). (2002). International ethical guidelines for biomedical research involving human subjects. Available at: http://www.cioms.ch/frame_guidelines_nov_2002.htm. Accessed: August 25, 2005.

Dresser, R. (2001). *When Science Offers Salvation: Patient Advocacy and Research Ethics*. New York: Oxford University Press.

Eisenberg, D., Davis, R., Ettner, S., Appel, S., Wilkey, S., Van Rompay, M., and Kessler. R. (1998). Trends in alternative medicine use in the United States, 1990-1997. *Journal of the American Medical Association* 280: 1569-75.

Eldredge, N. (1985). *Unfinished Synthesis: Biological Hierarchies and Modern Evolutionary Thought*. Oxford: Oxford University Press.

Emanuel, E., Wendler, D., and Grady, C. (2000). What makes clinical research ethical? *Journal of the American Medical Association* 283: 2701-11.

Emanuel, E. and Miller, F. (2001). The ethics of placebo-controlled trials–a middle ground. *New England Journal of Medicine* 345: 915-19.

Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine* 317: 382-83.

Greenberg v. Miami Children's Hospital, 264 F.Supp.2d 1064 (S.D. Fla. 2003).

Grimes vs. Kennedy Krieger Institute, Inc. 782 A.2d 807 (Md. 2001). Available at: http://www.courts.state.md.us/coa/2001/128a00.pdf

Health Insurance Portability and Accountability Act. (1996). *Pub. Law* 104-191.

Hoffman, D. and Rothenberg, K. (2002). Whose duty is it anyway?* The Kennedy Krieger opinion and its implications for public health research. *Journal of Health Care Law Policy* 6: 109-47.

Hrobjartsson, A. and Gotzsche, P. (2001). Is the placebo effect powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine* 344: 1594-1602.

ISEE. (1996). Ethical guidelines for environmental epidemiologists. Available at: http//:www.iseepi.org/ethguide.htm. Accessed: February 24, 2005.

Kionka, E. (1999). *Torts* (3rd ed.). St. Paul, MN: West Group.

Kopelman, L. (2000). Children as research subjects: a dilemma. *Journal of Medicine and Philosophy* 25: 745-64.

Kopelman, L. (2002). Pediatric research regulations under legal scrutiny: Grimes narrows their interpretation. *Journal of Law, Medicine, and Ethics* 38: 30-48.

Lavery, J., Upshur, R., Sharp, R., Hofman, K. (2003). Ethical issues in international environmental health research. *International Journal of Hygiene and Environmental Health* 206(4-5): 453-63.

Levine, R. (1988). *Ethics and Regulation of Clinical Research* (2nd ed.). New Haven: Yale University Press.

Lurie, P. and Wolfe, S. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337: 853-56.

Macklin, R. 2003. Bioethics, vulnerability, and protection. *Bioethics* 17: 472-86.

Mannino, D., Homa, D., Akinbami, L., Moorman, J., Gwynn, C., and Redd, S. (2002). Centers for Disease Control. Surveillance for Asthma --- United States, 1980--1999. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5101a1.htm. Accessed: August 19, 2004.

McCarthy, C. (1998). The evolving story of justice in federal research policy. In: Kahn J, Mastroianni A, and Sugarman J. *Beyond Consent: Seeking Justice in Research*. New York: Oxford University Press: 11-32.

Miller, F. and Brody, H. (2002). What makes placebo-controlled trials unethical? *American Journal of Bioethics* 2(2):3-9.

Miller, P. and Weijer. C. (2003). Rehabilitating equipoise. *Kennedy Institute of Ethics Journal* 13: 93-118.

Minkler, M., Blackwell, A., Thompson, M., and Tamir, H. (2003). Community-based participatory research: implications for public health funding. *American Journal of Public Health.* 93: 1210-3.

Moore v. Regents of the University of California, 51 Cal.3d 120 (1990).

Morgan, W., Crain, E., Gruchalla, R., O'Connor, G., Kattan, M., Evans, R., Stout, J., Malindzak, G., Smartt, E., Plaut, M., Walter, M., Vaughn, B., Mitchell, H. (2004). Results of a home-based environmental intervention among urban children with asthma. *New England Journal of Medicine* 351:1068-80.

Morin, K., Rakatansky, H., Riddick, F., Morse, L., O'Bannon, J., Goldrich, M., Ray, P., Weiss, M., Sade, R., Spillman, M. (2002). Managing conflicts of interest in the conduct of clinical trials. *Journal of the American Medical Association* 287: 78-84.

National Institute of Environmental Health Sciences. (1996). How do you study environmental health? Available at: http://www.niehs.nih.gov/oc/factsheets/fshow.htm Accessed: August 17, 2004.

National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. (1979). *The Belmont Report*. Available at: http://ohsr.od.nih.gov/guidelines/belmont.html. Accessed: August 20, 2004.

Nelson, R. (1998). Children as research subjects. In: Kahn J, Mastroianni A, and Sugarman J. *Beyond Consent: Seeking Justice in Research*. New York: Oxford University Press: 47-67.

Nelson, R. (2002). Appropriate risk exposure in environmental health research: the Kennedy Krieger lead abatement study. *Neurotoxicity and Teratology* 24: 445-49.

Nuremburg Code. (1949). In: *Trials of War Criminal before the Nuremburg Military Tribunals*. Washington: U.S. Government Printing Office, pp. 181-82.

Porter, R. (1999). *The Greatest Benefit to Mankind*. New York: W.W. Norton.

Ross, L. (2002). In defense of the Hopkins lead abatement study. *Journal of Law, Medicine and Ethics* 30: 50-55.

Resnik, D. (1998). The ethics of HIV research in developing nations. *Bioethics* 12: 286-06.

Resnik, D. (2001). Financial interests and research bias. *Perspectives on Science*: 8: 255-85.

Resnik, D. and Shamoo, A. (2003). Conflict of interest and the university. *Accountability in Research* 9: 45-61.

Resnik, D. (2004a). Disclosing conflicts of interest to research subjects: an ethical and legal analysis. *Accountability in Research* 11: 141-59.

Resnik, D. (2004b). Liability for institutional review boards: from regulation to litigation. *Journal of Legal Medicine* 25: 131-84.

Sackett, D., Straus, S., Richardson, S., Rosenberg, W., Haynes, R. (2000). *Evidence-Based Medicine: How to Practice and Teach EBM* (2nd Edition). London: Churchill Livingstone.

Schaffner, K. (2003). Research methodology: conceptual issues. In: Reich W (ed.). *Encyclopedia of Bioethics* (2nd ed.). New York: Simon and Schuster: 2270-77.

Shamoo, A. and Resnik, D. (2003). *Responsible Conduct of Research*. New York: Oxford University Press.

Sharp, R. (2003). Ethical issues in environmental health research. *Environmental Health Perspectives* 111: 786-8.

Sharp, R., Foster, M. (2000). Involving study populations in the review of genetic research. *Journal of Law, Medicine and Ethics* 28: 41-51.

Sober, E. (2000). *Philosophy of Biology* (2nd ed.). Boulder, CO: Westview Press.

Soskolne, C. and Light, A. (1996). Toward ethical guidelines for environmental epidemiologists. *The Science of the Total Environment* 184: 137-47.

Tauer, C. (1999). Testing drugs in pediatric populations: the FDA mandate. *Accountability in Research* 7: 37-58.

The Common Rule. (2001). 56 Fed Reg 28012. Codified in 45 C.F.R. 46 and 21 C.F.R. 50 and 56.

Varmus, H, and Satcher, D. (1997). Ethical complexities of conducting research in developing countries. *New England Journal of Medicine* 337: 1000-05.

Veatch, R. (1987). *The Patient as Partner: A Theory of Human Experimentation Ethics*. Bloomington: Indiana University Free Press.

Woodruff, P. and Fahy, J. (2001). Asthma: Prevalence, Pathogenesis, and Prospects for Novel Therapies. *Journal of the American Medical Association* 286:395-98.

World Medical Association. (2000) Declaration of Helsinki: ethical principles for medical research involving human subjects. *Journal of the American Medical Association* 284: 3043-45.

Wynia, M., Latham, S., Kao, A., Berg, J., Emanuel, L. (1999). Medical professionalism in society. *New England Journal of Medicine* 341:1612-1616.